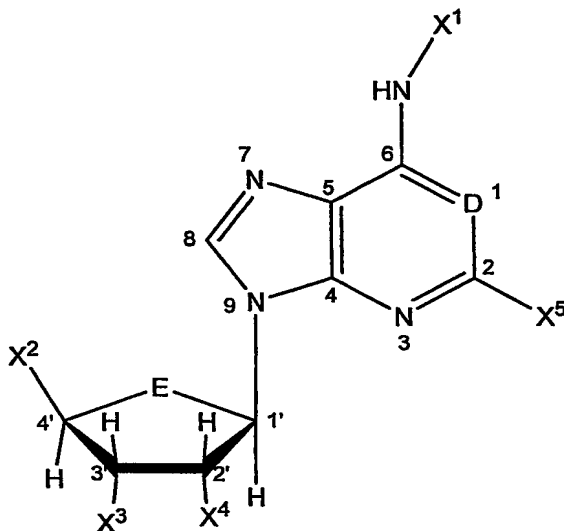


CLAIMS

1. A product which is a compound of the formula:



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wherein

D is N or CH;

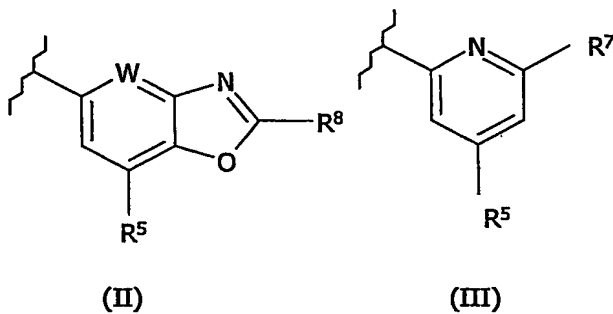
E is O, S or CH₂;

X¹ is a group of the formula -CR²⁰R²¹-CYCLE, where

10

R²⁰ and R²¹ are the same or different and H, F or CH₃;

CYCLE is of formula (II) or formula (III):



where:

R⁵ is iodine, bromine, methyl or trifluoromethyl;

- 15 R⁷ is H, halogen, C₁-C₁₀ acyl, OR¹¹, CO₂R¹¹ or CONR¹¹ where R¹¹ is C₁-C₁₀ hydrocarbyl optionally containing one or more in-chain and/or in-ring -O- linkages;

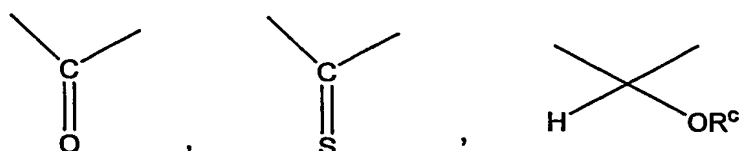
R⁸ is -NR⁹R¹⁰ or -COR⁹, where R⁹ and R¹⁰ are each independently methyl or ethyl; and

W is N or CH;

X^2 is hydroxymethyl, (C_1-C_3) alkoxymethyl, (C_3-C_5) cycloalkoxy methyl, carboxy, (C_1-C_3) alkoxycarbonyl, (C_3-C_5) cycloalkoxy-carbonyl, 1,1-aminoiminomethyl, 1,1-(mono-N- or di-N,N- (C_1-C_4) alkylamino)iminomethyl, 1,1-(mono-N- or di-N,N- (C_3-C_5) cycloalkylamino)iminomethyl, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylaminocarbonyl, mono-N- or di-N,N- (C_3-C_5) cycloalkylaminocarbonyl or N- (C_1-C_4) alkyl-N- (C_3-C_5) cycloalkylamino-carbonyl;

X^3 and X^4 are each independently hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, OR^a or NR^aR^b , where R^a and R^b are independently hydrogen, alkyl, aralkyl, carbamoyl, alkyl carbamoyl, dialkylcarbamoyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, or, when X^3 and X^4 are both OR^a , the two R^a groups together may form

10



where R^c is hydrogen or alkyl,



where R^d and R^e are independently hydrogen, alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

X^5 is H, halogen, (C_1-C_{10}) alkyl, fluorinated (C_1-C_{10}) alkyl (e.g. trifluoromethyl), (C_1-C_{10}) alkoxyalkyl, (C_1-C_{10}) alkoxy, (C_1-C_{10}) alkylether, (C_1-C_{10}) thioalkoxy, (C_1-C_{10}) alkylthio, amino, (C_1-C_{10}) alkylamino, $-COX^6R^{25}$ where X^6 is O or NH and R^{25} is (C_1-C_4) alkyl optionally terminally substituted by an aryl or a heteroaryl group and additionally or alternatively terminally substituted by hydroxy, (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl, or is (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl in either case terminally substituted by an aryl or heteroaryl group and, when having a terminal methylic carbon atom, optionally further terminally substituted by hydroxy,

or a pharmaceutically acceptable salt or prodrug thereof or a pharmaceutically acceptable salt of such a prodrug.

2. A product of claim 1, wherein

D is N;

30 E is O;

X^2 is mono-N- or di-N,N- (C_1-C_4) alkylaminocarbonyl, mono-N-

or di-, N- (C_3-C_5) cycloalkylaminocarbonyl or N- (C_1-C_4) alkyl-N- (C_3-C_5) cycloalkylaminocarbonyl;

X³ is OH or NH₂;

X⁴ is OH;

X⁵ is H, halogen, (C₁-C₁₀)alkyl, trifluoromethyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, or either of the latter two groups where terminally substituted as defined in claim 1.

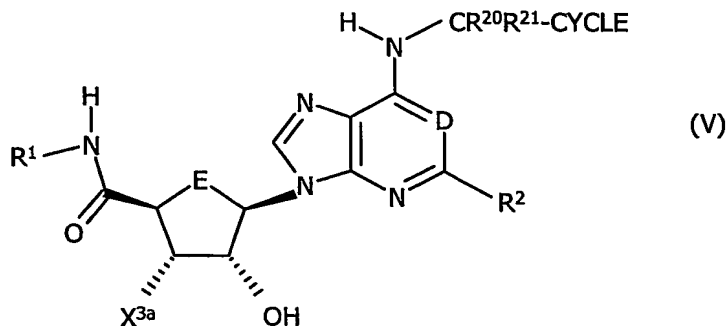
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3. A product of claim 1 or claim 2 wherein X⁵ is halogen.

4. A product of claim 3 wherein X⁵ is bromine or chlorine.

10 5. A product of any preceding claim wherein R²⁰ and R²¹ are both H.

6. A product of claim 1 wherein the compound is of formula (V):



where:

15 -CR²⁰R²¹-CYCLE, D and R² are as defined in claim 1;

E is O, S or CH₂ (e.g. E is O and optionally D is N and R² is Cl or other halogen);

R¹ is C₁-C₄ alkyl; and

X^{3a} is -OH or -NH₂.

20 7. A product of claim 6 wherein E is O.

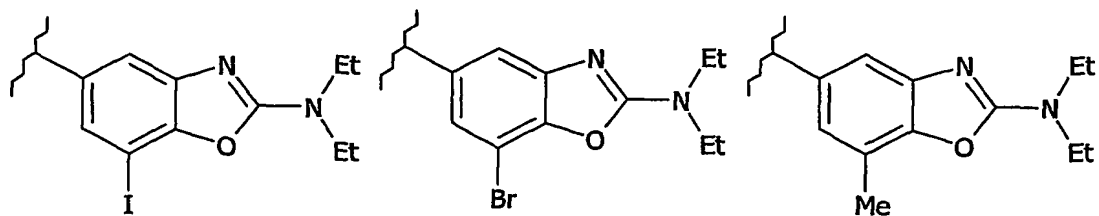
8. A product of any preceding claim wherein CYCLE is of formula (II).

9. A product of claim 8 wherein W is N.

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10. A product of claim 8 or claim 9 wherein R⁸ is dimethylamino or diethylamino.

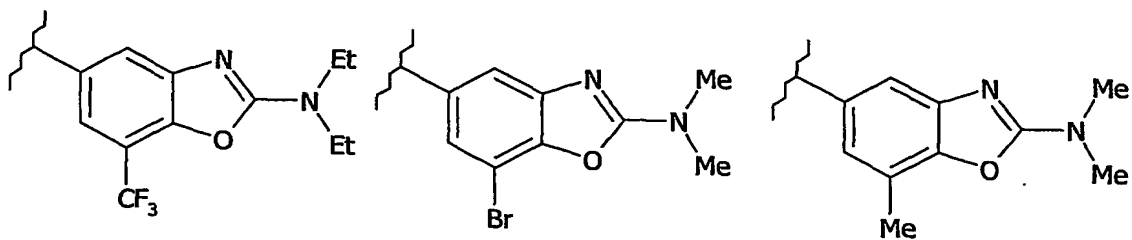
11. A product of claim 8 wherein CYCLE is selected from the group consisting of the following moieties:



(1)

(2)

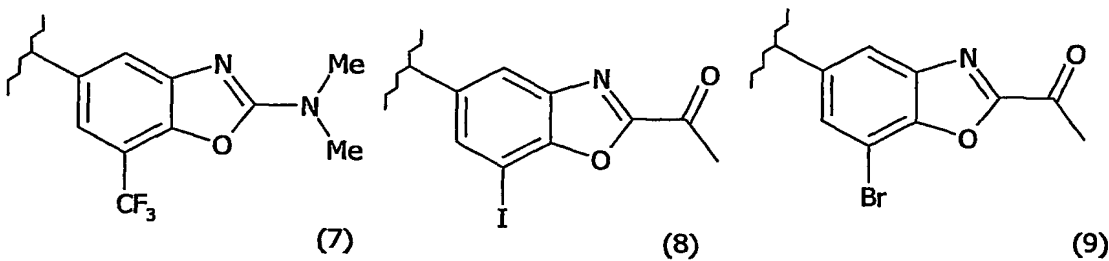
(3)



(4)

(5)

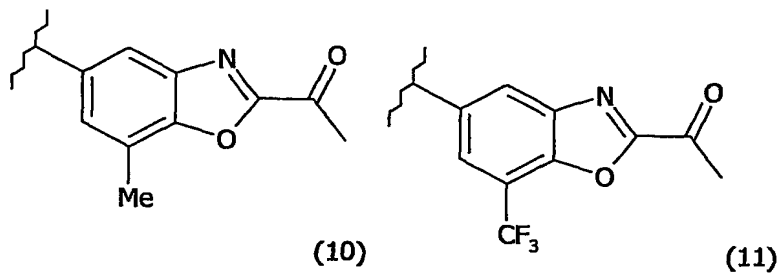
(6)



(7)

(8)

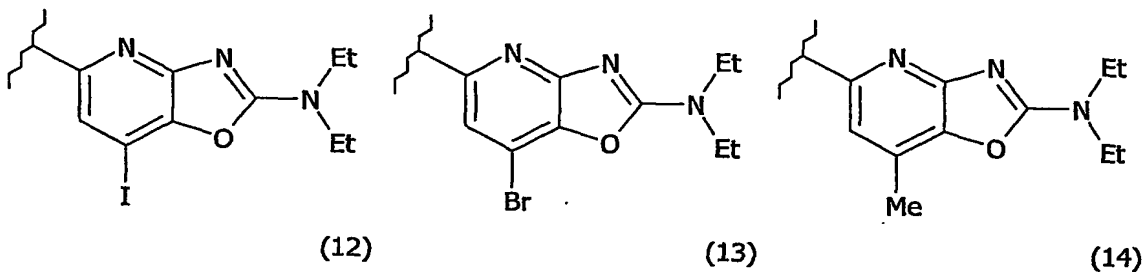
(9)



(10)

(11)

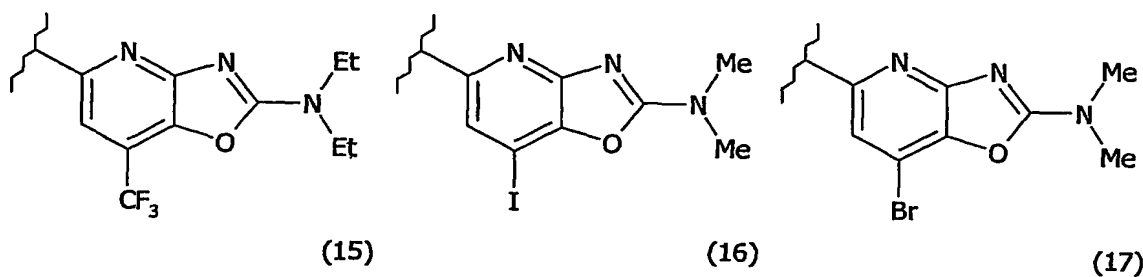
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(12)

(13)

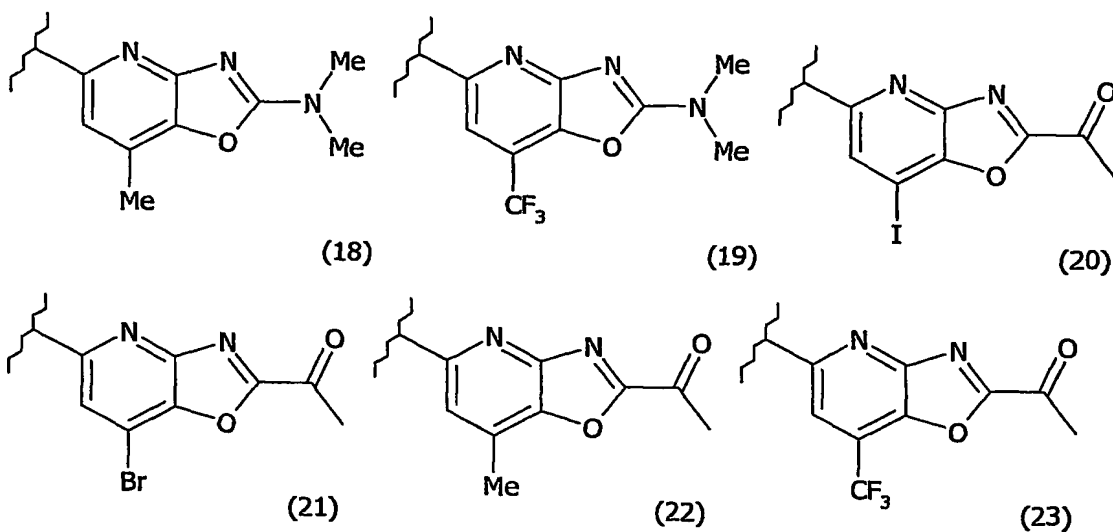
(14)



(15)

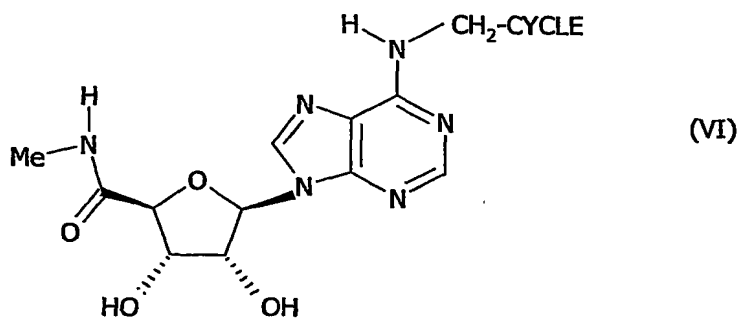
(16)

(17)



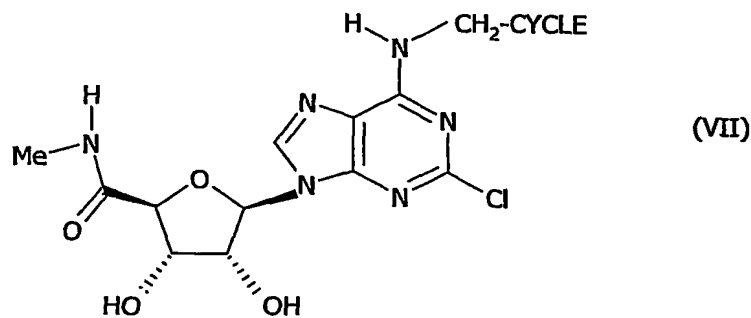
12. A product of claim 11 wherein CYCLE is of formula 1, 2, 3 or 4; or of formula 12, 13, 14
5 or 15.

13. A product of any of claims 8, 11 and 12 wherein the compound is of formula (VI):



10 where CYCLE is a group of formula (II).

14. A product of any of claims 8, 11 and 12 wherein the compound is of formula (VII):

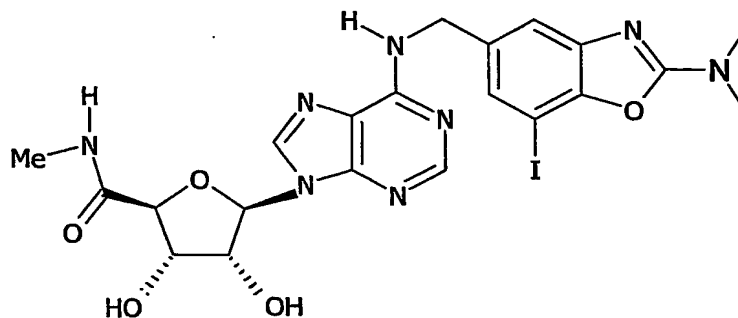


15 where CYCLE is a group of formula (II).

15. A modification of a product of claim 13 or claim 14 in which the 3' -OH group is replaced by another X^3 or X^{3a} group.

16. A product of any preceding claim in which the compound is not

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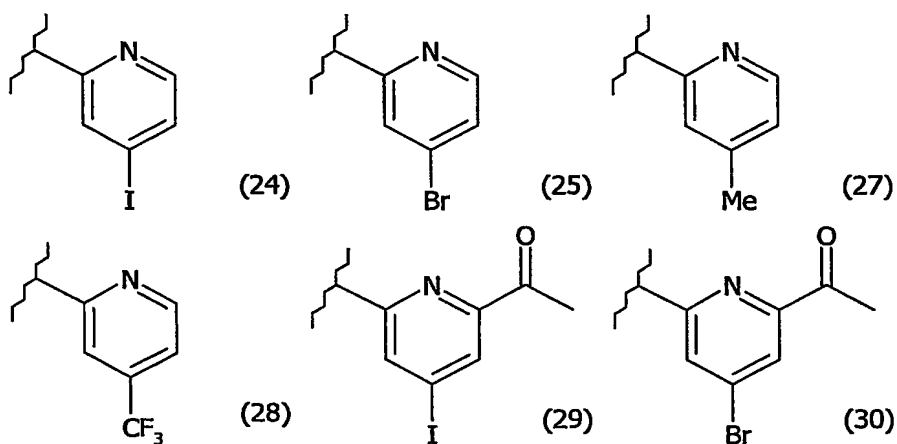
17. A product of any of claims 1 to 7 wherein CYCLE is of formula (III).

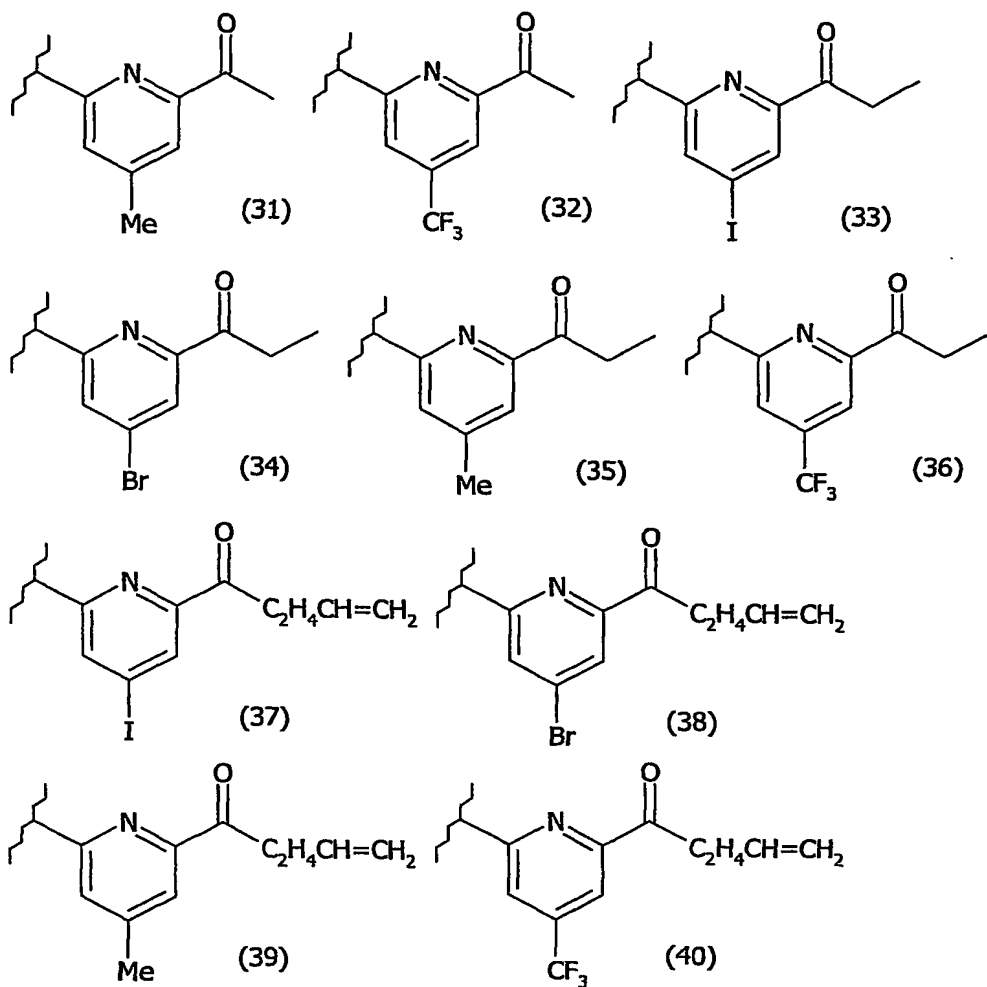
10 18. A product of claim 17 wherein R^7 is C_1-C_{10} acyl wherein acyl is $-COR^{12}$ in which R^{12} is hydrocarbyl or hydrocarbyl containing one or more in-chain and/or in-ring -O- linkages.

19. A product of claim 17 wherein CYCLE is selected from the group consisting of the following moieties:

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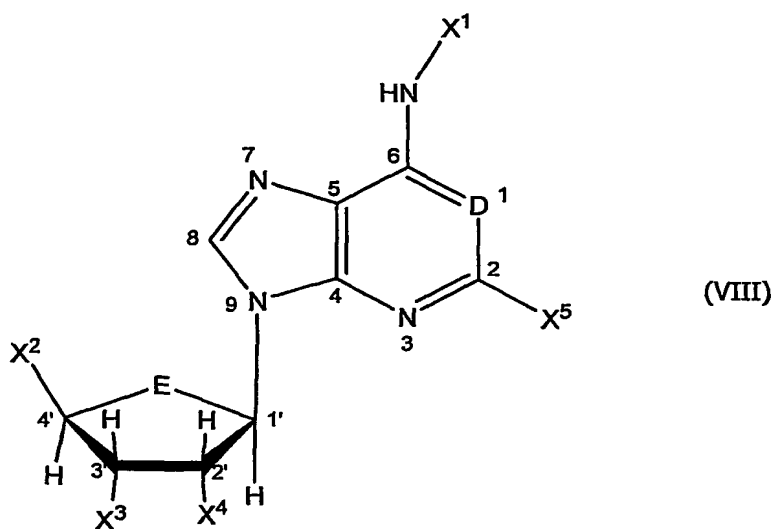
The invention therefore includes compounds having the following CYCLE moieties:





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20. A compound of formula (VIII):

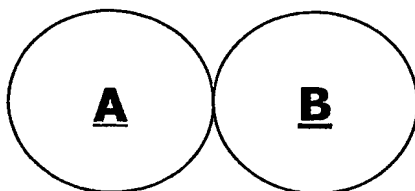


wherein

D is N or CH;

E is O, S or CH₂;

- X¹ is of the formula -CR²⁰R²¹-CYCLE where R²⁰ and R²¹ are the same or different and H, F or CH₃; and CYCLE is a bicyclic (fused) heteroaromatic ring of the formula



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wherein

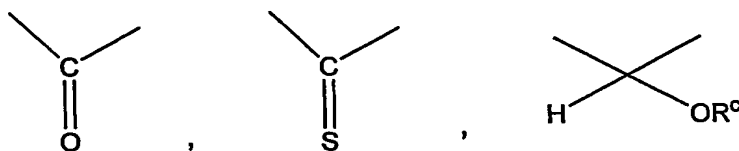
ring A is a 5- or 6- membered ring characterised by the following features (in which ring positions are numbered relative to the linkage to -CR²⁰R²¹-):

- i. a carbon atom at the 1-position;
- 15 ii. carbon atom as CH or a nitrogen atom at position 2;
- iii. it is 3, 4 fused to ring B;
- iv. the 5-position ring atom is substituted by a moiety R⁵ which is H, halogen, or an organic moiety having from 1 to 6 plurally valent atoms in addition to monovalent atoms selected from hydrogen and halogen;
- 20 v. If a 6-membered ring, it has at the 6-position a nitrogen, or -CM- where M is H, CH₃ or F;

ring B is a 5 or 6 membered ring characterised by the following features:

- (a) an in-ring heteroatom including O, N or S joined to the 4-position of ring A;
- (b) said in-ring heteroatom is joined within the ring secondly to a carbon which is substituted by a moiety R⁸ which is -N(C₂H₅)₂;
- 25 (c) an in-ring atom joined to the 3-position of ring A which is N, O, S or C, said C being in the form of a CH or CO group;
- (d) in the case of a 6-membered ring, the remaining ring member is nitrogen or carbon in the form of CH;
- 30 X² (the 4' substituent) is hydroxymethyl, (C₁-C₃)alkoxymethyl, (C₃-C₅)cycloalkoxy methyl, carboxy, (C₁-C₃)alkoxycarbonyl, (C₃-C₅)cycloalkoxycarbonyl, 1,1-aminoiminomethyl, 1,1-(mono-N- or di-N,N-(C₁-C₄)alkylamino)iminomethyl, 1,1-(mono-N- or di-N,N-(C₃-C₅)cycloalkyl-amino)iminomethyl, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylaminocarbonyl, mono-N- or di-N,N-(C₃-C₅)cycloalkylaminocarbonyl or N-(C₁-C₄)alkyl-N-(C₃-C₅)cycloalkylaminocarbonyl;
- 35 X³ and X⁴ are each independently hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, OR^aNR^aR^b, where R^a and R^b are independently hydrogen (most preferably X³ and X⁴ are OH), alkyl, aralkyl,

carbamoyl, alkyl carbamoyl, dialkylcarbamoyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, aryloxy carbonyl, or, when X^3 and X^4 are both OR^a , the two R^a groups together may form



where R^c is hydrogen or alkyl,

5



where R^d and R^e are independently hydrogen, alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

10

X^5 is H, halogen, (C_1-C_{10}) alkyl, fluorinated (C_1-C_{10}) alkyl (e.g. trifluoromethyl), (C_1-C_{10}) alkoxyalkyl, (C_1-C_{10}) alkoxy, (C_1-C_{10}) alkylether, (C_1-C_{10}) thioalkoxy, (C_1-C_{10}) alkylthio, amino, (C_1-C_{10}) alkylamino, $-COX^6R^{25}$ where X^6 is O or NH and R^{25} is (C_1-C_4) alkyl optionally terminally substituted by an aryl or a heteroaryl group [for example phenyl or a 5- or 6-membered heteroaryl group] and additionally or alternatively terminally substituted by hydroxy, (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl, or is (C_2-C_{10}) alkenyl or (C_2-C_{10}) alkynyl in either case terminally substituted by an aryl or heteroaryl group [for example phenyl or a 5- or 6-membered heteroaryl group] and, when having a terminal methylic carbon atom, optionally further terminally substituted by hydroxy.

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21. A compound of claim 20 wherein R^5 has from 1 to 4 plurally valent atoms.

22. A compound of claim 21 wherein the plurally valent atoms are selected from carbon, oxygen, sulfur and nitrogen.

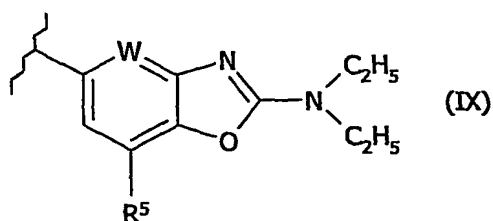
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23. A compound of claim 22 wherein R^5 is CH_3 , CF_3 , OH or NH_2 .

24. A compound of claim 20 wherein R^5 is H, I, Br or Cl.

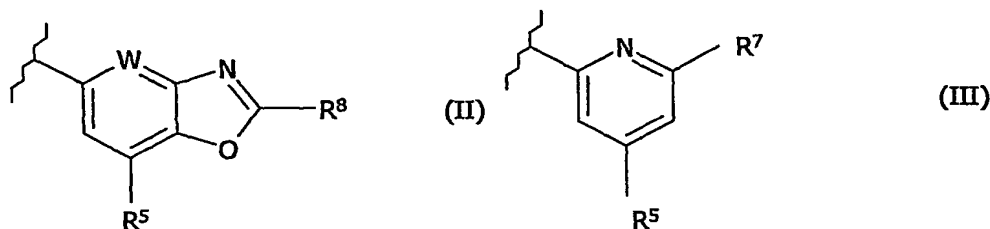
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25. A compound of any of claims 20 to 24 wherein CYCLE is of formula (IX)



26. A compound of any of claims 20 to 25 wherein where R^{20} and R^{21} are both hydrogen.

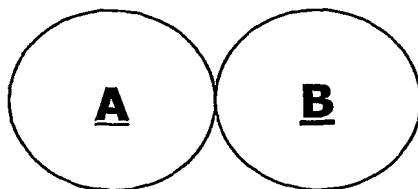
- 5 27. An adenosine analogue-type A3 receptor agonist having an N6 nitrogen substituted by a group of the formula $-CR^{20}R^{21}-CYCLE$ where R^{20} and R^{21} are the same or different and H, F or CH_3 ; and CYCLE is of formula (II) or formula (III):



where:

- 10 R^5 is iodine, bromine, methyl or trifluoromethyl;
 R^7 is H, halogen, C_1-C_{10} acyl, OR^{11} , CO_2R^{11} or $CONR^{11}$ where R^{11} is C_1-C_{10} hydrocarbyl optionally containing one or more in-chain and/or in-ring -O- linkages;
 R^8 is $-NR^9R^{10}$ or $-COR^9$, where R^9 and R^{10} are each independently methyl or ethyl; and
W is N or CH.
- 15 28. An adenosine analogue-type A3 receptor agonist having an N6 nitrogen substituted by a group of the formula $-CR^{20}R^{21}-CYCLE$ where R^{20} and R^{21} are the same or different and H, F or CH_3 ; and CYCLE is a bicyclic (fused) heteroaromatic ring of the formula

20



wherein

- ring A is a 5- or 6- membered ring characterised by the following features (in which ring positions are numbered relative to the linkage to $-CR^{20}R^{21}-$):
- 25

- i. a carbon atom at the 1-position;
- ii. carbon atom as CH or a nitrogen atom at position 2;
- iii. it is 3, 4 fused to ring B;

- iv. the 5-position ring atom is substituted by a moiety R^5 which is H, halogen or an organic moiety having from 1 to 6 plurally valent atoms in addition to monovalent atoms selected from hydrogen and halogen;
- v. if a 6-membered ring, it has at the 6-position a nitrogen, or $-CM-$ where M is H, CH_3 or F;
- 5 ring B is a 5 or 6 membered ring characterised by the following features:
- (a) an in-ring heteroatom including O, N or S joined to the 4-position of ring A;
- (b) said in-ring heteroatom is joined within the ring secondly to a carbon which is substituted by a moiety R^8 which is $-N(C_2H_5)_2$;
- 10 (c) an in-ring atom joined to the 3-position of ring A which is N, O, S or C, said C being in the form of a CH or CO group;
- (d) in the case of a 6-membered ring, the remaining ring member is nitrogen or carbon in the form of CH.
- 15 29. A product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28 for use as a medicament.
30. A product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28 for use in a method for selectively activating A_3 adenosine receptors in a mammal.
- 20 31. The use of a product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28 for the manufacture of a medicament for use in a method for selectively activating A_3 adenosine receptors in a mammal.
- 25 32. The use of a product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28 for the manufacture of a medicament for use for the reduction of tissue damage resulting from ischaemia or hypoxia.
- 30 33. The use of a product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28 for the manufacture of a medicament for use for preconditioning the heart to protect it from ischaemic damage.
34. The use of any of claims 31 to 33 wherein the medicament is for intravenous administration.
- 35 35. The use of any of claims 31 to 34 wherein the medicament is for use in combination therapy with another cardiovascular drug.

36. A pharmaceutical composition comprising a product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28.
37. A pharmaceutical composition of claim 36 which is an intravenous formulation.
- 5 38. The use in a medicament of an N6 substituent as defined in claim 27 or claim 28 to increase the A₃ receptor specificity of an adenosine analogue of which the remainder is compatible with the adenosine A₃ receptor for agonist use.
- 10 39. A method of stimulating adenosine A₃ receptors, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28.
- 15 40. A method of reducing tissue or organ damage (e.g., substantially preventing tissue or organ damage, inducing tissue or organ protection) resulting from ischaemia or hypoxia, comprising administering to a mammal in need of such treatment a therapeutically effective amount of an agent selected from a product of any one of claims 1 to 26 and agonist of claim 27 or claim 28.